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HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial

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Abstract

Objectives: We investigated the incidence of new non-vertebral fractures during HRT or low-dose vitamin (Vit) D supplementation in a 5-year prospective trial. Methods: A total of 464 early postmenopausal women, (a subgroup of the Kuopio Osteoporosis Study, \( n = 13100 \)) were randomized to four groups: (1) HRT, a sequential combination of 2 mg estradiol valerate and 1 mg cyproterone acetate; (2) Vit D (300 IU/day and 100 IU/day during the fifth year); (3) HRT + Vit D; and (4) placebo. Lumbar (L2-4) and femoral neck bone mineral densities (BMD) were determined by dual X-ray absorptiometry (DXA) at baseline, after 2.5 and 5 years of treatment. All new symptomatic non-vertebral, radiographically defined fractures were recorded. Results: Altogether, 368 women (79%) completed the 5 year treatment. In all, 32 women had 39 non-vertebral fractures during a mean of 4.3 year follow-up (HRT 4, Vit D 10, HRT + Vit D 8 and placebo 17). The reduction in the incidence of new non-vertebral fractures was significant in women with HRT alone (\( P = 0.032 \)) when adjusted by baseline BMD and previous fractures; observed also with the intention-to-treat principle (\( P = 0.048 \)). When the HRT groups were pooled, HRT showed a significantly lower incidence of new non-vertebral fractures (\( P = 0.042 \)) than women receiving placebo and also after adjusting as above (\( P = 0.016 \)); both in valid-case and in the intention-to-treat analysis. In the Vit D group, the fracture incidence was non-significantly decreased (\( P = 0.229 \)) in comparison with the placebo group. The estimated risk of new non-vertebral fractures among women treated with HRT alone was 0.29 (95% CI, 0.10–0.90) and with Vit D 0.47 (95% CI, 0.20–1.14) and with HRT + Vit D 0.44 (95% CI, 0.17–1.15), in comparison with the placebo group (adjusted by femoral BMD and previous fractures). Conclusions: This study is the first prospective trial confirming the beneficial effect of HRT on prevention of peripheral fractures in non-osteoporotic postmenopausal women. The effect of low-dose Vit D remains to be proved.

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Keywords: Fracture risk; Hormone replacement therapy; Osteoporosis; Menopause; Vitamin D

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1. Introduction

Osteoporosis is a disease of low bone mass leading to increased risk of fractures—primarily fractures of the hip, wrist and spine. The strongest predictor of fractures is reduced bone mineral density (BMD). Estrogen therapy can prevent bone loss in estrogen-deficient women. Case-control and cohort studies have shown that it can also prevent fractures among postmenopausal women [1–6]. However, there have not been any randomized trials of the effect of estrogen on non-vertebral fractures in postmenopausal women.

Vitamin D (Vit D) has been offered as a non-hormonal treatment for the prevention of osteoporosis. It seems to reduce bone loss among elderly women [7,8] but its effect on the prevention of osteoporotic fractures is contradictory [4,8,9]. Furthermore, no studies have reported the effect of Vit D on the fracture incidence in early postmenopausal, non-osteoporotic women.

We have conducted a 5 year randomized, clinical trial which was primarily undertaken in order to find out the effect of hormone replacement therapy (HRT) and low-dose Vit D on the BMD in non-osteoporotic early postmenopausal women. This paper reports the incidence of new non-vertebral fractures observed during this long-term prospective randomized study.

2. Materials and methods

The study population was a subgroup of the Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE), which started in 1989 with a postal inquiry sent to all 47–56 year old women \( n = 14220 \) of Kuopio Province, Eastern Finland. A total of 13100 women (92.8%) responded the questionnaire and in 1990–1991 BMD was measured in 3220 women, who were a random stratified sample of those willing to undergo bone densitometry. Interest in a 5 year clinical trial was ascertained and all the 464 willing, recently postmenopausal and eligible women were recruited for a 5 year clinical hormone trial (Fig. 1). Written informed consent was obtained from the participants, and the trial was approved by the ethics committee of the Kuopio University Hospital.

All women recruited were postmenopausal according to the criterion that 6–24 months had elapsed since their last menstruation. Exclusion criteria were restricted to contraindications for HRT; history of breast or endometrial cancer, thromboembolic diseases and medication-resistant hypertension. The women were randomized into four treatment groups (factorial design): (A) HRT group: sequential combination of 2 mg estradiol valerate, \( E_2\text{Val} \), (days 1–21) and 1 mg cyproterone acetate, CPA, (days 12–21), and a treatment-free interval (days 22–28) (Climen®, Schering AG); (B) Vit D group: Vitamin \( D_3 \) (cholecalciferol 300 IU), +93 mg Ca\(^{2+}\)/day, no intake during June–August (D-Calsor®, Orion), with the dose reduced to 100 IU/day during the fifth treatment year because of observed adverse lipid changes during Vit D treatment [10]; (C) HRT + Vit D group: treatments A + B combined; (D) Placebo group: calcium lactate, 500 mg/day (equivalent to 93 mg Ca\(^{2+}\)/day) (Calcium Lactate®, Rohto). No recommendations were given for the timing of the daily pills. Random allocation to study groups was carried out blockwise with computer—the block size being 4, 8 or 12. The personnel involved were unaware of the group allocation. However, after randomization the study was open for all treatment groups.

BMDs of the lumbar spine (L2-4) and left proximal femur (femoral neck) were measured using dual X-ray absorptiometry (DXA; Lunar, Madison, WI) at Kuopio University Hospital at baseline and after 2.5 and 5 years of treatment, by trained personnel. The short-term reproducibilities (coefficient of variation, CV%) of the spine and femoral neck measurements in our laboratory are 0.9 and 1.5%, respectively [11]. The long-term reproducibility (CV%) of our DXA instrument based on weekly repeated phantom measurements is 0.4% \( (n = 60) \). The BMD data was analyzed by one person without knowing the group allocation.

Each participant visited the out-patient clinic once a year when information about compliance and occurrence of new fractures was elicited. No attempt was made to exclude fractures on the basis of the degree of the trauma. However, there
were no fractures associated to car accidents of other major trauma. Reported symptomatic non-vertebral fractures were validated by medical records and radiographic reports. The dietary habits and other life-style factors of the subjects were determined by postal inquiry at baseline and after 5 years follow-up. The validity of the questionnaire was tested in part of dietary calcium intake. Dairy calcium covered 72–79% of the dietary calcium intake [12].

2.1. Statistical analysis

Statistical analysis was carried out using SPSS for Windows statistical package. The analyses were limited to non-vertebral fractures that occurred after the trial drug was initiated. The results are expressed as means with 95% confidence intervals (CI). $P < 0.05$ was regarded as statistically significant. The study power estimates were computed only for BMD changes and not for
Table 1
Baseline characteristics and laboratory measures in the 464 postmenopausal women according to treatment group

<table>
<thead>
<tr>
<th></th>
<th>HRT (n = 116)</th>
<th>Vit D (n = 116)</th>
<th>HRT+Vit D (n = 116)</th>
<th>Placebo (n = 116)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.9 (52.5–53.3)</td>
<td>52.8 (52.4–53.2)</td>
<td>52.5 (52.1–53.0)</td>
<td>52.6 (52.2–53.0)</td>
<td>0.624</td>
</tr>
<tr>
<td>Time since menopause (years)</td>
<td>1.1 (1.0–1.2)</td>
<td>1.1 (1.1–1.2)</td>
<td>1.1 (1.0–1.2)</td>
<td>1.1 (1.0–1.2)</td>
<td>0.971</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 (25.7–27.2)</td>
<td>26.6 (25.9–27.4)</td>
<td>26.3 (25.5–27.1)</td>
<td>26.1 (25.3–26.8)</td>
<td>0.670</td>
</tr>
<tr>
<td>Previous fractures during the last 15 years (%)</td>
<td>16 (14)</td>
<td>20 (17)</td>
<td>18 (16)</td>
<td>15 (13)</td>
<td>0.800b</td>
</tr>
<tr>
<td>Smokingb (pack-years)</td>
<td>9.2 (5.6–12.9)</td>
<td>6.0 (3.6–8.3)</td>
<td>8.5 (5.2–11.8)</td>
<td>8.3 (5.4–11.2)</td>
<td>0.651</td>
</tr>
<tr>
<td>Alcohol (absolute ethanol g/week)</td>
<td>24.8 (9.2–40.4)</td>
<td>19.8 (12.7–27.0)</td>
<td>16.2 (8.4–24.0)</td>
<td>22.3 (15.2–29.5)</td>
<td>0.566</td>
</tr>
<tr>
<td>Physically active persons (%)c</td>
<td>36 (31)</td>
<td>40 (35)</td>
<td>42 (37)</td>
<td>46 (40)</td>
<td>0.615d</td>
</tr>
<tr>
<td>Dairy Ca-intake (mg/day)</td>
<td>786 (717–855)</td>
<td>827 (752–902)</td>
<td>871 (785–957)</td>
<td>837 (759–915)</td>
<td>0.762</td>
</tr>
<tr>
<td>Lumbar BMD (g/cm²)</td>
<td>1.132 (1.104–1.160)</td>
<td>1.140 (1.112–1.168)</td>
<td>1.153 (1.123–1.183)</td>
<td>1.151 (1.122–1.179)</td>
<td>0.740</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>0.938 (0.915–0.961)</td>
<td>0.932 (0.911–0.954)</td>
<td>0.942 (0.921–0.963)</td>
<td>0.952 (0.932–0.973)</td>
<td>0.591</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>65.4 (54.8–76.0)</td>
<td>60.2 (55.8–64.7)</td>
<td>60.4 (55.2–65.5)</td>
<td>62.3 (57.3–67.2)</td>
<td>0.872</td>
</tr>
<tr>
<td>E₂ (nmol/l)</td>
<td>0.15 (0.11–0.18)</td>
<td>0.13 (0.10–0.17)</td>
<td>0.14 (0.12–0.17)</td>
<td>0.18 (0.10–0.25)</td>
<td>0.551</td>
</tr>
</tbody>
</table>

Values are given as the mean (95% CI).

a Kruskal–Wallis test.
b Smoking = life-time number of cigarettes/20 × 365.
c Physically active person, ≥3 h of physical activity /week.
d χ² test.

Fracture risk reduction because we did not expect that with this sample size and follow-up time a statistically significant reduction in the number of fractures could be attained.

The non-parametric Kruskal–Wallis test or the chi-squared test was used to analyze differences in baseline characteristics between the four groups and to compare women with fractures to those without fractures. Differences in BMDs between fracture and non-fracture groups were tested using Student’s t-test. Data on non-vertebral fractures were analyzed with the Cox proportional hazards model. In the analysis, the time to the first fracture was used. In order to examine the effect of HRT, the HRT and HRT+Vit D groups were pooled. The pooling of the data was considered valid on the basis of our previous observation that addition of low-dose Vit D to HRT does not increase the effect of HRT on BMD in non-osteoporotic early postmenopausal women [13]—a finding which was confirmed in our 5 year results (manuscript submitted). It is therefore most likely that both HRT and HRT+Vit D treatments reflect mainly the effect of HRT. The fracture-risk was analyzed in two ways; firstly using the data from the women who complied with the trial medication and secondly, with the intention-to-treat principle.
### Table 2

New non-vertebral fractures and site of fractures during the 5 year study period among the women who complied with the study treatment ($n = 368$). The values in the intention-to-treat analysis are shown in parenthesis ($n = 464$)

<table>
<thead>
<tr>
<th></th>
<th>HRT</th>
<th>Vit D</th>
<th>HRT + Vit D</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$ (at baseline)</td>
<td>116</td>
<td>116</td>
<td>116</td>
<td>116</td>
</tr>
<tr>
<td>Number of drop-outs</td>
<td>42</td>
<td>13</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Number of women with fractures</td>
<td>4 (6)</td>
<td>8 (11)</td>
<td>6 (7)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Number of fractures</td>
<td>4 (6)</td>
<td>10 (13)</td>
<td>8 (9)</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Cumulative% without fractures</td>
<td>95.3</td>
<td>92.1</td>
<td>93.9</td>
<td>85.8</td>
</tr>
<tr>
<td>Cumulative% without fractures in intention-to-treat analysis</td>
<td>94.6</td>
<td>89.1</td>
<td>93.8</td>
<td>85.6</td>
</tr>
<tr>
<td>Site of fractures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal radius/wrist</td>
<td>2 (2)</td>
<td>4 (6)</td>
<td>3 (3)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Ankle, foot or toe</td>
<td>2 (4)</td>
<td>4 (4)</td>
<td>2 (3)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Ribs</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Humerus</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hip</td>
<td>0 (1)</td>
<td></td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>1 (1)</td>
<td></td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Patella</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3. Results

The baseline characteristics of the women in the four treatment groups were similar (Table 1). Of the 464 women enrolled in the study, 368 (79%) completed the 5 year treatment (Fig. 1). There were 96 drop-outs, most of whom were from the HRT ($n = 42$) and HRT + Vit D groups ($n = 30$). The most common reasons for non-compliance were menstrual disorders such as hypermenorrhea, dysmenorrhea or metrorrhagia ($n = 19$) and headache ($n = 14$). As the study was designed for non-osteoporotic women, six osteoporotic women were withdrawn from this study, after enrollment when the data of subjects' eligibility was available (baseline lumbar or femoral BMD above 2 S.D. less than the mean of the whole study population). However, other diseases or medications possibly affecting BMD were accepted but there were no differences between the groups in the occurrence of these factors. Prospectively defined stopping rules were the same as the exclusion criteria in addition with initiation of new hormonal or calcitonine medication. After 5 years, all women were called for the 5 year BMD measurement. In all, 441 women (95%) came to the final visit. Three women had died from unrelated causes and twenty women were lost of follow-up.

In all, 39 symptomatic non-vertebral fractures occurred in 32 women during an average of 4.3 year follow-up period (range 0–5.9 years) with a reduced number of fractures in the groups with HRT or Vit D treatment. Seven women had two fractures (two in the HRT + Vit D group, two in the Vit D group and three in the placebo group) and only one woman had a symptomatic vertebral fracture. Table 2 shows the sites of fractures. Additionally, eight women among the drop-outs experienced a fracture between the period from the non-compliance to the final 5 year BMD measurement (HRT, 2 [ankle, toe], Vit D, 3 [wrist 2, hip 1], HRT + Vit D, 1 [toe] and placebo 2 [ankle 1, foot 1]). The other woman in the placebo group experiencing a second fracture.

In the analysis of the data of the women who complied with the study treatment ($n = 368$), the estimated risk of new non-vertebral fractures among women treated with HRT alone was 0.37 (95% CI, 0.12–1.12), with Vit D 0.59 (95% CI, 0.25–1.40) and with HRT + Vit D 0.48 (95% CI, 0.19–1.26), as compared with those receiving placebo. These differences did not achieve statistical significance ($P = 0.078$, 0.229 and 0.137, respectively). The independent effect of HRT on fracture risk was studied adjusting the relative hazards for baseline femoral neck BMD and previous fractures. Their addition to the model
Fig. 2. Cumulative fracture-free survival as a function of time to the first non-vertebral fracture. The reduction in the risk of non-vertebral fractures was significant in the HRT group (pooled) \( (P = 0.042) \) and non-significant in the Vit D group \( (P = 0.229) \), Cox proportional hazards model. HRT is shown as a continuous line.

showed a significant effect of HRT (HRT group, \( P = 0.032 \), Vit D group, \( P = 0.097 \) and HRT + Vit D group, \( P = 0.094 \)), the estimated risk of new non-vertebral fractures being 0.29 (95% CI, 0.10–0.90) in HRT group, 0.47 (95% CI, 0.20–1.14) in Vit D group and 0.44 (95% CI, 0.17–1.15) in HRT + Vit D, as compared with those receiving placebo. None of the other covariates tested altered the results. The difference in the incidence of fractures was more clearly significant \( (P = 0.042) \) when HRT and HRT + Vit D groups were pooled showing an estimated risk of fractures in HRT group 0.43 (95% CI, 0.19–0.97). Similarly the effect of HRT was significant when adjusted by baseline femoral neck BMD and previous fractures (HRT pooled \( P = 0.016 \), the estimated risk of new non-vertebral fractures being 0.37 (95% CI, 0.16–0.83). The difference in the cumulative proportions of women without non-vertebral fractures in the HRT and the placebo groups seemed to increase after the third year of treatment (Fig. 2).

When the data was analyzed with the intention-to-treat principle the estimated risk of new non-vertebral fractures among women treated with HRT alone was 0.41 (95% CI, 0.16–1.05), with Vit D 0.72 (95% CI, 0.33–1.56) and with HRT + Vit D 0.47 (95% CI, 0.19–1.16), as compared with those receiving placebo. These differences did not achieve statistical significance (HRT, \( P = 0.063 \), Vit D, \( P = 0.405 \), HRT + Vit D, \( P = 0.102 \)) as compared with the placebo. However, the effect of HRT was significant when adjusted by baseline femoral neck BMD and previous fractures (HRT, \( P = 0.048 \), Vit D, \( P = 0.276 \), HRT + Vit D, \( P = 0.110 \)) the estimated risk of new non-vertebral fractures being 0.38 (95% CI, 0.15–0.99) in HRT groups, 0.64 (95% CI, 0.29–1.42) in Vit D groups and, 0.48 (95% CI, 0.19–1.18) in HRT + Vit D group, as compared with those receiving placebo. Once again, when the HRT groups were pooled in the intention-to-treat analysis the estimated risk of fractures among women treated
with HRT was significantly reduced; 0.44 (95% CI, 0.21–0.93); \( P = 0.030 \) and also when adjusted by baseline femoral neck BMD and previous fractures; 0.43 (95% CI, 0.20–0.91, \( P = 0.027 \)).

Table 3 shows the data of women with and without fractures in each group. In the HRT group, the baseline lumbar and femoral neck BMDs were significantly lower \( (P = 0.014 \) and \( P < 0.001 \), respectively) in the women with fractures. Additionally, in the whole study group, significantly more women experiencing a fracture had the baseline femoral neck BMD in the lowest quartile \( (49\%, 19/39) \), \( P < 0.001 \), than women without a fracture. This difference could not be seen in the lumbar BMD \( (P = 0.237) \); data not shown. In the HRT group, the difference was notable both in the spine and femoral neck (Table 3).

4. Discussion

The results of our study show the beneficial effect of HRT in the prevention of non-vertebral fractures among non-osteoporotic early postmenopausal women already during a 5 year treatment. This finding is in accordance with previous studies which have shown that estrogen therapy can significantly decrease the number of osteoporotic fractures [3]—a conclusion based on observational studies [1,2,4,5]. In a prospective placebo-controlled study, Lufkin et al. [14] demonstrated that estrogen treatment can decrease the risk of vertebral fractures in osteoporotic women with previous vertebral fractures but our study is the first prospective randomized placebo-controlled trial for non-osteoporotic postmenopausal women. The reduction in the incidence of new non-vertebral fractures in the HRT group is also consistent with the increase in bone mass (lumbar BMD 1.8%/2.5 years, \( P < 0.001 \)) observed in our previous 2.5 year study [13] and in our 5 year results (manusc. submitted).

This study has an advantage of being both population-based and randomized. The group allocation was successful as there were no differences in the baseline characteristics tested and therefore, they could not bias the results. Even though the number of drop-outs in the HRT groups was greater than in non-HRT groups, the groups remained uniform. In addition the significance of the effect of HRT could be seen both in the analysis of the non-osteoporotic women who complied with the treatment and in the whole study group (intention-to-treat principle). Usage of a prospective and randomized study design has the advantage of minimizing the selection bias which is possible in both retrospective and cohort studies. Therefore, we believe our results are true and of great value in evaluating the benefits of HRT.

The independent effect of HRT alone could be demonstrated in multivariate model (both in valid-case and intention-to-treat analysis) with inclusion of baseline femoral neck BMD and previous fractures which were both significant covariates. In addition, a more pronounced effect of HRT could be shown when the HRT groups were pooled. This result mostly reflects the effect of HRT but it is still possible that Vit D has a minor effect of itself. Therefore, the data of the pooled HRT group emphasizes both the positive effect of HRT but also the importance of ensuring adequate Vit D intake even during HRT, especially for those who are Vit D deficient. However, it is most likely that the subjects in our study may not have been deficient with Vit D. This is supported by the results of the 1 year substudy of this trial [15] in which Vit D supplementation increased 25OHD concentrations significantly but did not affect the 1,25-(OH)\(_2\)D levels.

Cummings et al. [16] have reported that femoral neck BMD is the best predictor of hip fractures in comparison with BMDs of other sites. We have also shown that femoral neck BMD predicts non-vertebral fractures in perimenopausal women [17]. Similarly, the present study confirms the value of femoral neck BMD as a predictor of non-vertebral fractures. Sixty two percent of the women with a fracture in the HRT group (pooled) had the baseline femoral neck BMD in the lowest quartile. This implies that special emphasis should be focused on women with low femoral neck BMD also during HRT. However, the BMD changes obtained during a 5 year treatment did not differ among the women with or without
Table 3
Lumbar and femoral neck BMD data of the women with or without fractures among the 464 women during the 5 year trial (intention-to-treat)

<table>
<thead>
<tr>
<th></th>
<th>HRT group (pooled)</th>
<th>Vit D group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fx* (n = 13)</td>
<td>No Fx (n = 219)</td>
<td>Fx (n = 11)</td>
</tr>
<tr>
<td>Lumbar BMD at baseline (g/cm²)</td>
<td>1.041</td>
<td>1.149</td>
<td>0.014</td>
</tr>
<tr>
<td>FNc BMD at baseline (g/cm²)</td>
<td>0.821</td>
<td>0.947</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumbar BMD at 5 years (g/cm²)</td>
<td>1.020</td>
<td>1.159</td>
<td>0.006</td>
</tr>
<tr>
<td>FNc BMD at 5 years (g/cm²)</td>
<td>0.799</td>
<td>0.937</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumbar BMD change/5 year (%)</td>
<td>-1.1</td>
<td>0.8</td>
<td>0.274</td>
</tr>
<tr>
<td>FNc BMD change/5 year (%)</td>
<td>-1.5</td>
<td>-1.4</td>
<td>0.908</td>
</tr>
<tr>
<td>Lumbar BMD in the lowest quartile at the baseline (%)</td>
<td>7 (54)</td>
<td>50 (23)</td>
<td>0.023^{a}</td>
</tr>
<tr>
<td>FNc BMD in the lowest quartile at the baseline (%)</td>
<td>8 (62)</td>
<td>54 (25)</td>
<td>0.007^{a}</td>
</tr>
</tbody>
</table>

* Fx, fracture.
^{a} Independent samples t–test.
^{b} FN, femoral neck.
^{c} \chi^2 test (exact test).
fractures either among the compliers or in the whole study group. The limitation for this observation is the size of the study population which should be larger for more profound analysis.

Even though the number of fractures in the Vit D group was reduced compared with the placebo group, the reduction in the fracture incidence was non-significant. According to the previous studies, the effect of Vit D on the prevention of osteoporotic fractures is contradictory. Some studies have not found changes in the fracture incidence during Vit D treatment among the elderly [4,9], whereas slight positive effect has also been reported [8]. The true value of Vit D on the prevention of peripheral fractures in postmenopausal women remains to be proved. Possibly a more significant effect of Vit D might be found in an older population.

The results of our study might be criticized because we have not excluded any fractures according to trauma mechanism. Traditionally, an osteoporotic fracture has been considered to be caused by minimal trauma, such as a fall from standing height or less and other types of fractures have been excluded from analysis. We had a few fractures caused by a bicycle accident—no fractures caused by major trauma. We considered inclusion of all recorded fractures justified because it has also been shown that exclusion of high energy fractures might underestimate the incidence of osteoporosis [18] and therefore, it might also underestimate the effect of the treatment.

It has been suggested that HRT is more effective in preventing fractures if initiated within 5 years of menopause and if used for longer than 10 years [1,6]. The present study shows that even a shorter estrogen therapy may reduce the risk of non-vertebral fractures among non-osteoporotic early postmenopausal women.

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References


